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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/475,958	12/30/1999	Rex M. Bitner	16026-9038	7117

7590 11/13/2003

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/475,958	BITNER ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- Th MAILING DATE of this communication appears on th cover sh et with th c rrespondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Specification

1. The specification is objected to as documents have been improperly incorporated by reference. See page 11, first paragraph of the specification, and the amendment to paragraph beginning at page 11, line 27, wherein US Patent 6,310,199 is referenced for disclosing preferred embodiment. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

While the specification has been amended so to reflect the current status of application 09/312,172 (it is now issued US Patent 6,310,199), the specification does not identify with detailed particularity where that material is found in the cited documents (both foreign patent

document and cited US Patent). Accordingly, the document cannot be relied upon for satisfaction of enablement and written description elements of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The methods of independent claims 1, 7, 8, 15, 16, 19, and 21 place no limitation on the size of the particles used. Accordingly, the claims have been interpreted as encompassing the use of particles of virtually any size. A review of the disclosure fails to find support for an open-ended range of particle size. Page 12 of the original disclosure teaches the following:

> larger particles. The median particle size of the silica magnetic particles used in a particularly preferred embodiment of the present invention is about 1 to 15 μm, more preferably about 3 to 10 μm, and most preferably about 4 to 7 μm. The particle size distribution may also be varied. However, a relatively narrow monodal particle size

In view of the above teaching, the specification is considered to provide support for "silica magnetic particles" that range in size from "about 1 to 15 μm." The specification, however, is not considered to provide an adequate written description of silica magnetic particles of some other size.

4. Attention is directed to the following passage found at page 15 of the specification.

> One skilled in the art of the present invention will be able to use the teachings of the present disclosure to select and use magnetic particles other than the silica-based magnetic particles and ion exchange magnetic particles used to illustrate the methods and kits of the invention in the Examples, below.

It would appear that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description, which renders obvious a claimed invention, is not sufficient to satisfy the written description requirement of that invention.

5. For the above reasons, and in the absence of convincing evidence to the contrary, the specification does not provide an adequate written description of silica magnetic particles of any size other than those that fall within the range of "about 1 to 15 μm."

6. Claims 1-25 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004

(Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

7. For convenience, claims 1 and 7 are reproduced below.

1. (Twice amended) A method of using magnetic particles to concentrate or harvest cells, comprising the steps of:

(a) combining cells with magnetic particles, under conditions wherein the cells selectively adsorb directly to the particles thereby forming a complex [form a complex with the magnetic particles], wherein said magnetic particles are selected from the group consisting of (1) pH dependent ion exchange particles and (2) silica magnetic particles consisting essentially of a magnetic core coated with a siliceous oxide having a hydrous siliceous oxide adsorptive surface; and

(b) isolating the complex from the solution by application of magnetic force.

7. (Once Amended) A method of using magnetic particles to concentrate or harvest cells, comprising the steps of:

(a) combining cells with magnetic particles, under conditions wherein the cells selectively adsorb to the particles, thereby forming a complex, wherein the magnetic particles are pH dependent ion exchange magnetic particles selected from the group consisting of glycidyl-histidine modified silica magnetic particles and glycidyl-alanine modified silica magnetic particles; and

(b) isolating the complex from the solution by application of magnetic force.

8. For purposes of examination, claims 1-7 have been interpreted as encompassing a method whereby any specific cell (be it of bacterial, plant or animal origin; living or dead; hydrated or desiccated), or combination of cells can be "concentrated or harvested." Said sample(s) or source(s) from which said cell or cells are to be "concentrated or harvested" has been interpreted as encompassing that which is highly heterogeneous mixture.

9. A review of the specification identified the following examples.

- Example 1, page 16, Gel Electrophoresis
- Example 2, pages 16-17, Absorption Spectrophotometry
- Example 3, pages 17-19, Synthesis of Glycidyl-Histidine and Glycidyl-Alanine Silica Magnetic Ion Exchange Particles
- Example 4, pages 19-20, Preparation of a Lysate of Plasmid DNA
- Example 5, pages 20-21, Lysate Clearance by Centrifugation or Silica Magnetic Particles, Followed by Plasmid DNA Isolation using Glycidyl-Histidine or Glycidyl-Alanine Silica Magnetic Particles
- Example 6, pages 21-23, Lysate Clearance with Silica Magnetic Particles or Varying Amounts of Mag-IE-Glycidyl-Histidine Particles

- Example 7, pages 24-26, Lysate Clearance by Centrifugation vs. Using Silica magnetic Particles, followed by Isolation of Plasmid DNA from Cleared Lysate using Silica Magnetic Particles
- Example 8, pages 26-28, Concentration of cells, Lysate Clearing, and DNA Isolation Using Mag-IE-Glycidyl-Histidine Particles
- Example 9, pages 28-30, Clearing Mouse Tissue Homogenates using Mag-IE-Glycidyl-Histidine Particles and isolating DNA and RNA therefrom using Mag-IE-Glycidyl-Histidine Particles
- Example 10, pages 30-36, Concentration of White blood Cells, Lysate Clearing, and DNA Isolation from whole Blood using Mag-IE-Glycidyl-Histidine Particles, Nonporous MAGNESIL-IE-GLY-Histidine Particles, and MAGNESIL^{TM} Particles using Human Whole Blood

10. Claims 1-7 require the use of pH-dependent ion exchange matrices. Page 11 of the specification directs one to US Patent 6,310,199 as disclosing the preferred embodiment of using pH-dependent ion exchange ligands. Page 11, reads in part:

> Such preferred ion exchange ligands and pH dependent ion exchange matrices which incorporate such ligands are described in US Patent Application Ser No. 09/312,172, now U.S. Patent No. 6,310,199, for an invention titled pH DEPENDENT ION EXCHANGE MATRIX AND METHOD OF USE IN THE ISOLATION OF NUCLEIC ACIDS, incorporated by reference herein, an application filed concurrently with the provisional patent application on which the present non-provisional patent application is based.

11. As noted above in the objection to the specification, said US patent has not been properly incorporated by reference. Accordingly, the U.S. patent cannot now be relied upon to satisfy the enablement and written description requirements of 35 USC 112, first paragraph. Example 8,

pages 26-28, of the disclosure, is most relevant to the invention of claims 1-7. Here the specification teaches that multiple and separate aliquots of Mag-IE-glycidyl-histidine particles were used to first bind unidentified "cells" and that subsequent to lysis, that "Mag-IE-glycidyl-histidine " were used to bind the nucleic acid. The specification does not teach that the second aliquot was in the form of magnetic particles. The specification does not teach what type of cell was used in the example. The example does teach that DNA was being isolated. Such a showing does not support the position that any target nucleic acid could be isolated, be it a specific DNA sequence in a mixture of DNA, or be the nucleic acid mRNA, tRNA or rRNA, or mitochondrial DNA.

12. Claims 21-25 and 27-29 are directed toward a "method of isolating a target nucleic acid." Said claims 21-25 and 27-29 have been interpreted as allowing for the binding of a "target nucleic acid" while not binding other nucleic acids that are also present. For convenience, claim 21 is reproduced below.

21. (Twice amended) A method of isolating a target nucleic acid from a disrupted biological material, comprising the target nucleic acid, a first non-target material, and a second non-target material, comprising the steps of:

(a) combining a solution of the disrupted biological material with first magnetic particles under conditions wherein the first non-target material selectively adsorbs directly to the particles, thereby forming [forms] a first complex [with the first magnetic particles], wherein said magnetic particles are selected from the group consisting of (1) pH dependent ion exchange particles and (2) silica magnetic particles consisting essentially of a magnetic core coated with a siliceous oxide having a hydrous siliceous oxide adsorptive surface;

(b) separating the first complex from the solution of disrupted biological material by application of magnetic force, forming a cleared solution comprising the target nucleic acid and the second non-target material;

(c) combining the cleared solution with second magnetic particles under conditions wherein the target nucleic acid adsorbs to the second magnetic particles, forming a second complex;

(d) isolating the second complex from the cleared solution;

(e) washing the second complex by combining the second complex with a wash solution and separating the second complex from the wash solution by magnetic force; and

(f) combining the washed second complex with an elution solution, under conditions wherein the target material is desorbed from the second magnetic particles.

13. As seen in the claim, *supra*, the method requires the use of "first magnetic particles" and "second magnetic particles." And that it is the 'second magnetic articles" that are used to isolate the "target nucleic acid" from the now-cleared solution.

(c) combining the cleared solution with second magnetic particles under conditions wherein the target nucleic acid adsorbs to the second magnetic particles, forming a second complex;

The claims do not recite any limitation that would require the first and second magnetic particles to be different from one another. Accordingly, the claims have been interpreted as encompassing the use of but one type of magnetic particle to perform all functions. Additionally, the claims have been interpreted as encompassing the isolation of one specific nucleic acid sequence when present in a broadly heterogeneous mixture of nucleic acids.

14. Example 7 is perhaps the most relevant to the method of Claims 21-25 and 27-29. As seen therein, "cells" are used, but the disclosure does not describe just what type of cell was being used. The lysis buffer used in Example 7 reasonably suggests that the cells were that of a bacterial culture. Additional support has been found for using mouse tissue and human blood as starting material. The specification is effectively silent, however, with regard to how plant material is to be treated.

15. The specification has not been found to support and enable the position that any specific "target nucleic acid" can be isolated from any sample over that of any other nucleic acid. The specification has been found to support the position that total DNA and a mixture of cellular RNA with genomic DNA can be isolated via binding to MAGNESIL-IE-Glycidyl-Histidine Particles, Nonporous MAGNESIL-IE-GLY-Histidine Particles, and MAGNESIL^{TM} Particles (Example 10).

As shown above, the claims encompass embodiments not adequately described by the disclosure. It is well settled that one cannot enable that which they do not yet possess, including that which may be obvious. The embodiments encompassed by the claims clearly relate to chemical and physiological processes, which is an area of art long recognized as being

unpredictable and deserving of greater level of disclosure so to enable the full scope of the claims. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

17. Applicant is urged to amend the claims such that they more closely parallel the disclosure provided.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 1-6, 8-14, 21-25 and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. Claims 1-6, 8-25, and 27-29 are indefinite with respect to how cells "selectively absorb directly to the particles" (emphasis added) when it appears that the cells are binding to a "hydrous siliceous oxide adsorptive surface." Such a surface speaks to there being a chemical moiety between the "pH dependent ion exchange particles" or the "silica magnetic particles" and the cell. Such chemical moiety would in effect proscribe "direct" adsorption, but would accommodate indirect adsorption.

21. Claims 1-6, 8-25, and 27-29 are indefinite with respect to whether the "pH dependent ion exchange particles" or the "silica magnetic particles", or both of said types of particles "consists

essentially of a magnetic core coated with a siliceous oxide having a hydrous siliceous oxide adsorptive surface."

22. Claim 8 is confusing where in line 4 reference is made to a "second magnetic particle" without there being any reference to a first magnetic particle. Claims 9-14, which depend from claim 8, fail to overcome this issue and are similarly rejected.

23. Claim 21 recites the limitation "the particles" in lines 5-6. There is insufficient antecedent basis for this limitation in the claim. Applicant is urged to consider amending the claim to recite --the first magnetic particles--. Claims 22-25 and 27-29, which depend from claim 21, fail to overcome this issue and are similarly rejected.

Claim Rejections - 35 USC § 102

24. The rejection of claims 1, 3, 4, and 6 under 35 USC 102(b) is withdrawn.

25. The rejection of claims 1-25 and 27-29 under 35 U.S.C. 102(e)(f) is withdrawn.

Claim Rejections - 35 USC § 103

26. The rejection of claims 1-7, 21-25 and 27-29 under 35 U.S.C. 103(a) is hereby withdrawn.

Conclusion

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

28. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

29. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
10 November 2003